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TITLE: Improving Synchronization and Functional Connectivity in Autism Spectrum Disorders through Plasticity-Induced Rehabilitation Training

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Improving Synchronization and Functional Connectivity in Autism Spectrum Disorders Through Plasticity-Induced Rehabilitation

ANNUAL TECHNICAL PROGRESS REPORT

August 1, 2010 – July 31, 2011

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ANNUAL TECHNICAL PROGRESS REPORT

I. Introduction

This project is investigating the functional correlates of Autism Spectrum Disorder (ASD) with the goal of developing strategies to reduce cognitive, behavioral, and neurofunctional deficits. The primary goal is to test a model of the neural basis for changes in ASD induced by QEEG-guided plasticity-induced rehabilitation training. This intervention will help characterize the effects of altering cortical dynamics via operant conditioning of specific EEG frequencies on the amelioration of ASD symptoms and its impact on matched, typically developing children in a double-blind study. It will help characterize the specific cognitive, behavioral, electrophysiological, and functional brain changes that occur with such training. The outcome will provide evidence for a link between “mirroring” activity in the human brain, EEG mu rhythms that reflect large-scale processing, and behaviors that comprise the core deficits in ASD. Furthermore, the project will help identify behavioral phenotypes that may contribute to diagnosis of the disorder and help predict successful treatment outcomes.

II. Body

Project Location. This project involves only human subjects and initially was to take place at two study sites: The University of California, San Diego (UCSD) and San Diego State University (SDSU). The PI, Dr. Jaime A. Pineda, is faculty in the Department of Cognitive Sciences at UCSD and is responsible for all components of the project related to quantitative electroencephalogram (QEEG)-guided plasticity-induced rehabilitation training, including recruitment of autism spectrum disorder (ASD) and typically developing (TD) participants, pre- and post-training assessment, protocol preparation and testing, rehabilitation training, data analysis, and preparation for publication. The Co-Investigator, Dr. Ralph-Axel Mueller is faculty in the Department of Psychology at SDSU and is responsible for all components of the project related to neuroimaging, including preparation of functional magnetic resonance imaging (fMRI) designs and data acquisition protocols, contact and scheduling of participants for imaging sessions, mock scanning sessions (where appropriate), acquisition of structural and functional magnetic resonance (MR) images, preprocessing of MR imaging data, statistical analyses of functional MRI data (whole brain and region-of-interest analyses), and preparation for publication.

Protocol Approval. Preparation and submission of the paperwork to get the protocol approved began as soon as notice of the award was received. We started IRB protocol approval process at UCSD in January 2010 and received approval four months later in May 2010. We then submitted to CDMRP the protocol entitled "Improving Synchronization and Functional Connectivity in Autism Spectrum Disorders Through Plasticity-Induced Rehabilitation Training" (Proposal Number AR093335, Award Number Pending, HRPO Log Number A-16018.a). However, a number of issues arose that led to various delays in the start of the project.

Problem #1. We were delayed for approximately two months, until August 1, 2010, at the very start primarily due to missing or delayed documentation (e.g., Facility Safety Plans for both UCSD and SDSU), as well as problems with the protocol approval process.

Problem #2. We had at the outset requested money for neuroimaging scans on the main grant since costs to Dr. Pineda, as a UCSD faculty, would be slightly less at the UCSD Keck Center (where scanning takes place). Unfortunately, a series of local misunderstandings led to requesting that this money, post-award, be directly allocated to the subcontractor. Because the request was approved, we were then in the unfortunate position of paying a higher rate for use of the scanner at UCSD. We set about reversing this but it led to a couple more months of delay.

Problem #3. Since PIRT or neurofeedback training is to be guided by a quantitative analysis of the EEG, it was necessary to set up a process for recording, analyzing, and implementing training protocols based on the outcome of the QEEG. We decided it was best to send the EEG data to an expert in the field for that type of analysis. Unfortunately, we did not initially budget sufficient funds for this aspect of the

proposal. It took several months to negotiate a deal with Dr. Jack Johnstone of Q-Metrx on the most cost-effective method to do this but our lack of funds led to our requests given very low priority. Subsequently we negotiated a better deal at a satisfactory price for QEEG analyses with another service provider - Dr. Jay Gunkelman of Q-Pro. Additionally, we have received a UCSD Senate grant to help cover these costs.

Problem #4. We have run into several technical problems with the bioamplifiers and impedance sensors that are part of the Thought Technology neurofeedback system. A combination of some breakdowns in the training of the RAs and the delicate nature of some of the hardware has contributed to this problem. Thought Technology has been very responsive to our problems and has provided temporary loaner equipment while correcting the malfunctions within a reasonable time frame.

Problem #5. Perhaps the most serious delay occurred from another misunderstanding. Thinking that because we had local approval from the UCSD IRB for all aspects of the project we could start the recruitment process before the final approval of the protocol had been received from CDMRP. On March 28, 2011 we were notified of our noncompliance. According to the Provision 4 in the Assistance Agreement it is prohibited to enroll human subjects without the HRPO approval. A stop payment was placed on funding until such approval occurred. A major issue developed in that in order to increase participant accrual we had established a partnership with a center in the Los Angeles area where we hoped to replicate the work being conducted at UCSD in San Diego. However, we first needed to modify the university's FWA to include this new research center in order for research to officially begin there. After many rounds we finally got local approval for the change in the FWA and subsequently received HRPO approval on August 4, 2011.

Participant Recruitment. These efforts began in August 2010 (as described above in Problem #5). There were three parts to this effort: advertise and recruit, select participants, administer pre-training assessments.

- Advertise and recruit participants: This process involved producing and distributing ads and flyers, talking to various autism groups in San Diego, and contacting parents in our database who had previously participated in other studies at UCSD. We also advertised on the Autism Speaks website and other such websites. Finally, we contacted both our consultant, Dr. Alan Lincoln, who is Director of the San Diego Center for Autism Research, Evaluation and Service (CARES) and our collaborator, Dr. Ralph Axel-Mueller at SDSU, for referrals to our project. These efforts identified an initial set of children with ASD who met the criteria for participation and whose parents showed a willingness to be in the study. We also identified several typically developing (TD) children for the control group.
- Selection of participants: Verification of diagnosis, carried out by Dr. Lincoln, involved the administration of various clinical assessments: Autism Diagnostic Observation Schedule or ADOS, Autism Diagnostic Interview or ADI, and Wechsler Abbreviated Scale of Intelligence or WASI. ASD participants are

evaluated to determine if they meet inclusion criteria for high functioning autism.

- Pre-training assessment: Once identified, participants are scheduled for cognitive, behavioral and electrophysiological assessments. These include evaluation of the Mu Suppression Index (MSI), quantitative EEG (QEEG), test of variable attention (TOVA), Emotion Discrimination, Autism Treatment Evaluation Checklist (ATEC), additional paper and pencil tests, and neuroimaging. All participants are evaluated in the same way.

Unfortunately problems developed from the beginning of our recruitment efforts. Parents and children found it much more difficult to participate during the school year than during the summer months and thus our accrual of subjects slowed down considerably after September. Therefore, as noted above, in order to increase participant accrual we formed a partnership with the Speech and Language Development Center (SLDC) located in Buena Park, California (2 hrs north of the UCSD campus) to essentially duplicate our efforts there. SLDC offers a readily available pool of children on the spectrum, who attend the school, as well as TD children. To date, we have a total of 8 ASD and 6 TD participants enrolled in the study at the UCSD site. There are 3 ASD and 1 TD participants enrolled at the SLDC site.

Set Up and Testing of Protocols at Study Sites. This has required setting up and testing hardware and software for the plasticity-induced rehabilitation training (PIRT) at UCSD and SLDC, as well as testing protocols for neuroimaging at SDSU/UCSD. Personnel at SLDC who will administer clinical assessments have been identified, trained and certified. SLDC Research Assistants who will administer and score outcome measures, electrophysiological tests and neurofeedback training have been trained. Paper and pencil assessments, software tools, and protocol design have been set up at SLDC. Neurofeedback hardware and software implementation, protocols, testing of procedures, and training of personnel are completed and we have begun testing participants. Neuroimaging protocols have also been successfully tested.

At the beginning of the project we had identified a School Psychologist, Sally Miller, to help verify the diagnosis of autism (ADI, ADOS) for each high functioning autistic child recruited to the study at SLDC. Sally had received initial training by Dr. Alan Lincoln (our consultant) and subsequently was certified by *WESTERN PSYCHOLOGICAL SERVICES (WPS)*, which is approved by the American Psychological Association (APA) to sponsor continuing education for psychologists. Ms Miller was also to administer the IQ test (Wechsler Abbreviated Scale of Intelligence or WASI) while also training SLDC personnel to administer these assessments themselves. More recently Ms Miller has moved from the area and is not able to continue this work. Fortunately, Dr. Lincoln has arranged for the Los Angeles CARES office to provide the testing for the SLDC population, just as the San Diego CARES office is providing the testing for our San Diego population.

Training of Research Assistants. We have begun training Research Assistants at UCSD

and SLDC to provide PIRT to our participants. We have completed two rounds of training at both centers. Currently there are approximately 6-8 RAs who have received the training and have begun actual neurofeedback sessions. They were trained to administer and score the behavioral, cognitive, and electrophysiological outcome measures and administer neurofeedback training. We have also identified two individuals dedicated specifically for scheduling the training times with parents and participants and making sure at least two trained RAs are available during the sessions.

Behavioral and Cognitive Outcome Measures

- *Test of Variable Attention (TOVA)*, the visual continuous performance task that has been normed in the general population is used to assess sustained attention.
- *Autism Treatment Evaluation Checklist (ATEC)*, a parental checklist is used to evaluate ASD treatment paradigms based on four subscale scores (speech/language/communication, sociability, sensory/cognitive awareness, health/physical/behavior) and a total score, which are weighted according to the response and the corresponding subscale.
- The *Behavior Assessment System for Children (BASC)* is a comprehensive tool that provides information about a child's behaviors and emotions. It includes a parent rating scale and self-report of personality. The BASC attempts to measure both problem and adaptive behaviors.
- The *Vineland Adaptive Behavior Scales* is a valid and reliable test to measure a person's adaptive level of functioning. The content and scales are organized within a three-domain structure: Communication, Daily Living, and Socialization.
- The *Gilliam Autism Rating Scale (GARS)*, a parental/child parallel screening tool for ASD for individuals between the ages of 3 and 22. It is designed to help differentiate those with autism from those with severe behavioral disorders, as well as from those who are typically developing. It is a norm-referenced instrument that reflects the conceptualizations of autism as defined in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* and the Autism Society of America (1994).
- The *Social Responsiveness Scale (SRS)* provides a quantitative metric of the type and severity of impairments in social functioning that are characteristic of ASD children with five subscales (receptive, cognitive, expressive, and motivational aspects of social behavior plus autistic preoccupations).

Electrophysiological Outcome Measures

- *Quantitative EEG*. High-density recordings of the brain's electrical activity are measured and quantified to guide neurofeedback treatment. Participant's EEG are recorded in two conditions of eyes open and eyes closed. Conditions are randomly presented for a total of 9-10 minutes per condition. QEEG analysis involves comparison with a normative database and helps to identify the sites of greatest atypical EEG.

- *Mu Suppression Index (MSI)*. The MSI was developed by Oberman (Oberman et al., 2005), and is used to assess changes in mu power in response to the observation of movement. The standard protocol is followed (i.e., participants view silent action videos, 120 s, on a computer monitor while counting the number of pauses in the action). The test consists of a baseline condition and three experimental conditions.
- *Emotion Discrimination Task (EDT)*. A modification of the Eyes task described by Baron-Cohen et al. (Baron-Cohen et al., 1997) has been designed to assess ASD responses to faces and the emotions expressed by such stimuli, as such processing is atypical in ASD (Chawarska & Shic, 2009; Scherf et al., 2008; Hadjikhani et al., 2007). Each trial is preceded by a fixation cross for 2 seconds. A cue photo of a face then appears at the top of the screen for 2 seconds. Three additional 'match' face photos then appear at the bottom of the screen. Participants are instructed to press the keyboard button corresponding to the photo that matches the emotional expression of the cue photo.

QEEG-Guided PIRT (Neurofeedback) Training. All participants receive 90 minutes of PIRT per week. They are trained for 20 weeks for a total of 30 hours of training. The recording sites used for initial training is identified as those showing abnormal activity in the QEEG. PIRT involves recording EEG activity and using the modulation of that activity to control aspects of a video game or to control playing of a DVD movie. The approach requires keeping the EEG rhythms in a specific frequency range above a pre-determined threshold while keeping EMG activity and other specified EEG frequencies below a pre-defined threshold. On the screen participants see a display of at least three threshold bars alongside the video game window. One corresponds to the rewarded frequency and the other two correspond to inhibited frequencies. Rewards (i.e., if the video game is a racing car, the car will move or a DVD movie will play if the thresholds are met) are given based on satisfying two conditions: 1) power in appropriately identified band exceeds a specified threshold, and 2) power from the theta (related to blinks) and high frequency gamma (related to muscle movement) activity is inhibited and falls below a specified threshold. Theta and gamma inhibition feedback is included in the design for two reasons. First, it ensures that individuals in the experimental group cannot advance in the game or play the DVD by producing movement-induced power increases in the entire EEG spectrum. Second, it allows us to distinguish improvement effects as a function of EEG modulation, modulation of autonomic nervous system activity, or placebo effects.

Neuroimaging. The problem in terms of having to pay higher rate for scanner time at UCSD has been corrected. This required us to essentially undo a re-budgeting effort and essentially return to the original budget proposed for this project. A number of ASD and control participants have already been successfully scanned to date as part of the pre-training assessment protocol. Some participants require training with a mock scanner to desensitize them to the scanning equipment. The entire imaging session lasts approximately 1-hr per participant and involves the following:

- 6-min echo planar imaging (EPI) resting state scan
- Three 5-min EPI task runs (the task is an imitation task)
- A spoiled gradient recalled (SPGR) high-resolution anatomical scan
- 8-min diffusion tensor imaging scan
- 3-slice magnetic resonance spectroscopy (MRS) scan

We have begun preliminary data processing and analysis of the data collected so far.

Post-Training Assessment: No one to date has completed the training phase. Nonetheless, following completion of 30 hrs of training, we will begin scheduling and administering the post-training cognitive, behavioral, and electrophysiological assessments. These are the same tools used in the pre-training assessment phase (MSI, QEEG, TOVA, Emotion Discrimination, ATEC, other paper and pencil tests, and neuroimaging). All ASD and TD children undergo these assessments.

Data Processing and Analysis. We are in the data collection phase of the project and have not yet started analysis of the data.

Preparation and Submission of Journal Article(s). We are not at the point of preparing any type of manuscript based on the work from this project.

Integration of Project Findings & Preparation of R01 Application. This will be done towards the end of the project.

III. Key Research Accomplishments

- An additional research center in Buena Park, CA, the Speech and Language Development Center, has been established to allow for increased accrual of participants
- HRPO approval has been obtained
- Intense recruitment efforts have begun and are only slightly behind schedule given the long delay to get the project started
- Mechanisms for recruiting, selecting, and assessing participants are in place and working
- Hardware and software for the neurofeedback training at UCSD and SLDC have been acquired, piloted, and are working
- Training of Research Assistants has been successful
- Protocols and procedures for the neuroimaging part of the project are in place and have been tested successfully

IV. Reportable Outcomes

We are only in the data collection phase of the project, given the long delay in getting HRPO approval, therefore no reportable outcomes are available at this time. We will be seeking a no-cost extension to be able to successfully complete the project.

V. Conclusion

The work completed to date will allow us to very quickly move into and complete the data collection part of the project with minimal problems. An additional research center will increase participant accrual and potentially minimize the dropout rate. No changes to the protocol methods and processes in place are recommended at this time.

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VII. Appendices

None